

# Rofecoxib-Associated Upper Gastrointestinal Bleed:

## A Case Report

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### Abstract

To our knowledge, this is the first clinical report of a rofecoxib-associated upper gastrointestinal hemorrhage. We urge caution in prescribing rofecoxib to patients with risk factors for peptic ulcer disease and recommend limiting the dose to 25 mg per day for these patients.

**Key Words:** Rofecoxib, cyclo-oxygenase-2 inhibitor, nonsteroidal anti-inflammatory drug, peptic ulceration, upper gastrointestinal bleed.

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### Introduction

GASTROINTESTINAL (GI) MORBIDITY is a major complication associated with the use of nonspecific cyclo-oxygenase (COX)-inhibiting nonsteroidal anti-inflammatory drugs (NSAIDs). In the US there are 20,000 hospitalizations and 2,600 deaths reported per year. The risk of hospitalization and mortality for GI complications is about 1–1.5% and 0.13% per year respectively (1, 2).

COX activation results in prostaglandin production, which mediates important physiological functions. NSAIDs attenuate prostaglandin synthesis by nonspecifically inhibiting COX activity (3). While this nonspecific inhibition attenuates the prostaglandin-mediated peripheral nociceptor sensitization, there is a high incidence of gastrointestinal (GI) complications.

Two isoforms of COX have been identified, COX-1 and COX-2. COX-1 is a constitutive enzyme, primarily responsible for the production of prostaglandins that regulate many physiologic processes, including gastrocytoprotection (4). COX-2 is an enzyme induced by inflammatory stimuli and results in the production of prostaglandins that mediate the inflammatory response and sensitize peripheral nociceptors (5). The new class of NSAIDs, COX-2 specific inhibitors such as rofecoxib, exhibit minimal COX-1 inhibition. Theoretically, se-

lective COX-2 inhibition leads to analgesia and anti-inflammatory effects, while minimizing GI complications. We present a case of a rofecoxib-associated upper GI bleed.

### Case Report

The patient is a 48-year-old male with a history of rheumatoid arthritis and Crohn's disease. He had been treated intermittently for fifteen years with prednisone for his Crohn's disease; the last treatment was approximately one year ago. The patient's medical history was significant for peptic ulcer disease diagnosed six years prior to presentation. Esophago-gastroduodenoscopy (EGD) and cultures for *Helicobacter pylori* were negative one year ago. The patient reported no tobacco, alcohol or recreational drug use. His daily medications included omeprazole, clonazepam, and 8 tablets of oxycodone 4.5 mg/aspirin 325 mg for the past fifteen years for pain relief from his Crohn's disease and rheumatoid arthritis.

One month prior to his most recent hospitalization, the patient presented with an exacerbation of his rheumatoid arthritis. The patient started to take rofecoxib 25 mg once daily, but the dose was increased to 25 mg twice daily by his rheumatologist in order to optimize analgesia and further decrease inflammation. Six days later, the patient experienced abdominal pain and vomited "coffee ground" material. Rofecoxib and oxycodone/aspirin were discontinued. An EGD revealed a peptic ulcer of the gastric antrum. The patient's abdominal pain and GI bleeding resolved with conservative management. To relieve his chronic pain, oxycodone 5

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mg every 4 hours was recommended when required. After discharge from the hospital, the patient began to self-medicate with aspirin 325 mg per day. After he consulted with his gastroenterologist, rofecoxib was discontinued and oxycodone/aspirin therapy was restarted, because of the patient's insistence that this combination was the only means of relieving his chronic pain. Since the above incident, the patient has had good pain control and no further GI distress.

### Discussion

Rofecoxib, 4-[4-(methylsulfonyl)phenyl]-3-phenyl-2(5H)-furanone, inhibits COX-2 800 times more than COX-1 *in vitro*. *In vivo*, rofecoxib shows dose-related inhibition of COX-2 but no significant COX-1 inhibitory action (6). This selectivity maintains the beneficial effects of COX-1 on the gastrointestinal tract, i.e., increased gastric blood flow, decreased acid secretion and increased gastric mucus secretion, while inhibiting the COX-2 effects of inflammation and pain.

The most commonly reported GI symptoms of patients receiving rofecoxib included epigastric discomfort, diarrhea, and nausea (7). Based upon studies of 1,516 patients, the six-month cumulative incidence of gastroduodenal ulcers in patients taking rofecoxib 25 mg daily was 4.3%; the incidence was 7.5% with rofecoxib 50 mg daily, 25.7% with ibuprofen 2400 mg daily, and 4.7% with placebo (8, 9). These endoscopic studies included patients who were older than 65 years, and patients with a history of GI bleeding, perforation, ulcer, baseline gastroduodenal erosions and active *Helicobacter pylori* infection. These patients had no evidence of active gastroduodenal ulcer at the commencement of the respective studies. Neither study included patients on aspirin-containing medications.

The incidence of GI bleeding with rofecoxib may be lower than the incidence of peptic ulceration in the general population. A study looking at the geometric mean amount of daily fecal red blood cell (RBC) loss in healthy volunteers showed rofecoxib to cause a similar amount of RBC loss compared with placebo, and approximately half the volume of RBC loss relative to the nonspecific COX inhibitor, ibuprofen (10). Among 3,357 patients studied for up to one year and treated with varying daily doses of rofecoxib of up to 50 mg, there were 19 cases of peptic ulcer bleeding, only 3 of which were considered serious upper GI events, using protocol-derived criteria, for a cumulative incidence of 0.09% (11).

To our knowledge, our case report is the first reported description of a GI bleed associated with rofecoxib use. The selective inhibition of COX-2 makes this class of medications inherently much safer than the traditional nonspecific NSAIDs. However, as noted in the above discussion of endoscopic studies, the incidence of gastroduodenal ulcers in patients taking rofecoxib 50 mg daily is greater than with placebo, albeit much less than with nonspecific COX-inhibiting NSAIDs. With this in mind, our case report emphasizes the need for caution in prescribing rofecoxib to patients who have had active peptic ulcer disease at one time or another, or a history suggestive of peptic ulcer disease in association with previous use of steroids or NSAIDs. Also, it is our opinion that the daily dose of rofecoxib probably should not exceed 25 mg in a patient at risk for GI ulcer disease. Further studies are needed to determine the safe daily dose range for rofecoxib and to elucidate the relationship between predisposing ulcerogenic factors and rofecoxib-induced GI pathology.

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